Increase in knee muscle strength is associated with a decrease in activity limitations in established knee osteoarthritis: A 2 year follow-up study in the Amsterdam Osteoarthritis (AMS-OA) cohort.

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Abstract

Objective. To examine the association between changes in knee muscle strength (extensor and flexor muscles separately, and averaged) and changes in activity limitations in patients with established knee osteoarthritis (OA) at two years.

Methods. Data from 186 patients with knee OA part of the Amsterdam Osteoarthritis cohort were gathered at baseline and at two-year follow up. Knee extensor and knee flexor muscle strength were assessed using an isokinetic dynamometer. Activity limitations were assessed using Western Ontario and McMaster University Osteoarthritis Index (WOMAC) - Physical Function subscale, Get Up and Go test (GUG) and the 12-steps stairs test. Uni- and multivariate linear regression analyses were used to assess the association between changes in muscle strength and changes in activity limitations, adjusting for relevant confounders and baseline activity limitations.

Results. There was an overall 16% increase in mean knee muscle strength ($p<0.001$), 19% increase in knee extensor muscle strength ($p<0.001$) and 17% increase in knee flexor muscle strength ($p<0.001$) at two years. Increased average knee muscle strength and knee flexor muscle strength were associated with better self-reported physical function (WOMAC) ($b=-5.7$, $p=0.03$ and $b=-6.2$, $p=0.05$), decreased time performing the GUG ($b=-1.2$, $p=0.003$ and $b=-1.4$, $p=0.05$) and decreased time performing the stairs test ($b=-4.4$, $p<0.001$ and $b=-6.6$, $p<0.001$). Increased extensor muscle strength was only associated with decreased time performing the stairs test ($b=-2.7$, $p<0.001$).

Conclusion. Increase of knee muscle strength, mainly in knee flexors, was associated with decreased activity limitations in patients with knee OA at two years. These results suggest that muscle strength may partially explain the between-patients variability in activity limitations.

Key-words: knee osteoarthritis, muscle strength, activity limitations.

Introduction

Osteoarthritis (OA), the most common form of arthritis affecting synovial joints, is considered a major cause of pain and activity limitations (1). Activity limitations are defined as difficulties in performing daily activities (2). Previous studies have shown a slow increase in activity limitations over time in patients with OA (3), while others have found no change or even a decrease in activity limitations in this group of patients (4;5) Nevertheless, there is a high between-patients variability in the course of activity limitations in patients with OA which needs to be further explained (6;7).

Muscle strength is considered a relevant determinant of activity limitations in patients with knee OA (5). The cross-sectional relationship between low muscle strength and activity limitations has been reported extensively (5;8). Moreover, earlier studies have shown baseline muscle strength in patients with OA as potential predictor for activity limitations in the long term (4;6;9;10). The longitudinal association between a decrease in muscle strength and an increase in activity limitations has been studied in two observational studies, which showed conflicting results (4;11), and in one clinical trial which failed to control for relevant confounders (12). Overall, there is scarce evidence about the longitudinal association between muscle strength and activity limitations in absence of a well-defined intervention, in patients with established knee OA. Testing the longitudinal association between muscle strength and activity limitations in knee OA is a direct and necessary extension beyond cross-sectional research in this area.

Previous studies have focused mainly on the association of knee extensor muscle strength and activity limitations, and limited attention has been given to the role of knee flexor muscle strength in activity limitations in patients with OA. However, in this group of patients an appropriate muscle strength of knee extensor as well as flexor muscles is important for stability of the knee and prevention of joint stress (13). The aim of the study was to examine the association between changes in knee muscle strength (extensor and flexor muscles separately, and averaged) and changes in activity limitations in patients with established knee OA at two years. We hypothesize that in patients with established OA an increase in knee extensor and knee flexor muscle strength, as well as an increase in average knee muscle strength, would be associated with a decrease in activity limitations in the long term.

Patients and Methods

Patients

One hundred and eighty six patients from the Amsterdam Osteoarthritis (AMS-OA) cohort (127 females, 59 males) with unilateral or bilateral diagnosis of knee OA according to the American College of Rheumatology (ACR) (15) were included in this study. The AMS-OA is a cohort of patients with OA of the knee and/or hip (16;17), who have been referred to an outpatient rehabilitation centre (Reade, Centre for Rehabilitation and Rheumatology; Amsterdam, the Netherlands) (14;18). In the present study, the group of patients was defined as established knee OA due to the combination of confirmed diagnosis of knee OA according with the ACR criteria and the presence of OA related problems which motivated the patients to look for specialized care. Patients were assessed by rheumatologists, radiologists and rehabilitation physicians. Exclusion criteria were rheumatoid arthritis or any other form of inflammatory arthritis (i.e., crystal arthropathy, septic arthritis, spondyloarthropathy), and total knee replacement during the follow up period. Two years after the baseline assessment patients were invited to the follow up assessment (Figure 1). Demographic, radiographic, clinical, psychosocial and biomechanical factors related to OA were assessed at baseline and at two-year follow up. The assessment of muscle strength and physical performance was completed by the same two trained movement scientists following an established and approved protocol. At follow-up, the data collectors did not have information on baseline assessment. Only patients who completed the assessment at both times were included in the study. All patients provided written inform consent according to the declaration of Helsinki. The study was approved by the Reade Institutional Review Board.

Measures

Muscle strength. Knee muscle strength was assessed concentrically using an isokinetic dynamometer (EnKnee, Enraf-Nonius, Rotterdam, Netherlands) at baseline and at two-year follow up (18). An initial practice attempt was used for the patients to get familiar with the required movements. The patients performed three maximal test repetitions to measure the isokinetic strength of the knee extensor muscles (mainly quadriceps) and knee flexor muscles (mainly hamstrings) for each knee, at 60°/second. Mean values of knee muscle strength (average knee extensor and flexor combined, as well as mean knee extensor and mean flexor muscle strength (separate) per leg were calculated (Nm) and divided by the patient's weight (kg) (19). This measure (in Nm/kg) has shown an excellent intrarater reliability (ICC 0.93) in knee OA patients (20). Muscle strength parameters were averaged over the two legs due to the fact that 132 (71%) patients included in the study had OA in both knees and muscle strength in the two legs was highly correlated in our group of patients (r=0.82, p=0.01). In addition, optimal muscle strength in both legs is required for an appropriate performance of ambulatory activities of daily living.

Activity Limitations. Activity limitations were assessed using the Western Ontario and McMaster Universities Osteoarthritis physical function index subscale (WOMAC-PF), a self-reported questionnaire, and two physical performance tests (Get Up and Go test (GUG) and the stairs test).

The WOMAC questionnaire was used to evaluate self-reported activity limitations, stiffness and pain in patients with OA (21). It has five items related to pain and two related to stiffness. The physical function (PF) section is composed of 17 items and each one might be scored from 0 to 4, given a possible total score from 0 to 68. Higher scores represent more activity limitations. A validated Dutch version of WOMAC (22) was used in this study.

The GUG test (23;24) was performed with patients sitting on a high standard chair (49cm). Patients were told to stand up without help of the arms on the command "go", and walk 15 metres through an unobstructed corridor as fast as possible, without running. The chronometer was stopped when they reached a mark on the floor. All patients were wearing walking shoes. Patients who normally used walking devices were allowed to use them during the test. A longer time (seconds) taken to perform the test was considered a higher activity limitation.

In the stairs test (18), patients were instructed to climb 12 stairs (16cm high) going one stair at the time as fast as possible, but not running. Patients were encouraged not to use the handrail, but were not prohibited from doing so for safety. Once they reached the top, the chronometer was stopped while they turned around. Subsequently and following the same instructions, after a signal, the chronometer started again while the subjected descended the stairs. Both times in seconds were recorded independently and then added to calculate the time for the whole task. All patients were wearing comfortable walking shoes. A longer time performing the test was considered a higher activity limitation.

Potential confounders. Demographic data (i.e., age and gender) were recorded. Information related to comorbidities was collected with the Cumulative Illness Rating Scale (CIRS) (25). This instrument allows to gather information related to 13 body systems, scoring from 0 (none) to 4 (extremely severe) according to the severity of the condition. The number of diseases on which the patients scored a severity of 2 or higher was calculated and incorporated in the analyses. Body Mass Index (BMI) was calculated as body mass in kilograms divided by height in meters squared (kg/m^2). C-reactive protein (CRP) (mg/l) levels were measured in serum from patients' blood samples and processed immunoturbidimetrically using CRPLX test kits (26-28) and the Roche Cobas-6000 analyser. Non steroid anti-inflammatory drugs (NSAID) use was dichotomised (yes, no). Pain level was assessed using the WOMAC pain subscale (21). Additionally, at two-year follow up the patients were asked if they had received physiotherapy treatment at any institution or if they took part in a study involving physical therapy intervention during the past two years.

Statistical analysis

Descriptive statistics were used to characterize the study population at baseline and at two-year follow up. Percentages were used for categorical variables, medians (inter-quartile ranges (IQRs)) and means (standard deviations (SDs)) for continuous variables. McNemar tests and paired t-tests were used to analyse the differences in the distribution of the variables at baseline and at two-year follow up.

The baseline- two-year follow up change score was calculated for knee muscle strength (extensor and flexor muscles separately, and averaged) and activity limitations (WOMAC-PF, GUG and stairs test). The association between change in muscle strength (Nm/kg) and change in activity limitations was analysed using linear regression (analysis of covariance) (29). First, regression analyses were used to explore the association between change in muscle strength and change in activity limitations at two-year follow up, adjusting for baseline activity limitations (crude models) (29). Second, relevant confounding was defined as 10% change in the crude regression coefficient of the central determinant, after adjustment for an additional variable (30). The confounding effect of other variables possibly affecting the association between muscle strength and activity limitations (i.e., age, gender, change in comorbidities, change in NSAID use, change in BMI, change in CRP levels, change in WOMAC pain and physical therapy treatment) was evaluated based on a 10% difference between crude and adjusted regression coefficient. Third, fully adjusted multivariable regression models including all relevant confounding variables were analyzed.

Statistical significance was accepted at p-values < 0.05. All analyses were performed using SPSS software, version 18.0 (SPSS, Chicago, IL).

Results

Patients. A total of 268 patients with knee OA that completed the baseline assessment were invited to participate in the follow up evaluation. Eight percent of the patients (n=21) were excluded from the study due to total knee replacement. From the eligible patients who met the inclusion criteria at follow up (n=247), 25% (n=61) declined the invitation for various reasons. Figure 1 shows the patients flow during the study. There were no significant differences in baseline characteristics between the groups of patients who were and were not part of the two-year follow up assessment (Table 1).

Descriptives. Demographic and clinical characteristics of patients who participated at baseline and at two-year follow up (n=186) are shown in Table 2. Sixty eight percent of the study group (n=127) were women. Mean±SD age at baseline was 61±7.3 years. In the study group, there was an overall 16% increase in mean knee muscle strength mean±SD (0.08±0.2Nm/kg; $p<0.001$), 19% increase in knee extensor muscle strength (0.11±0.3Nm/kg; $p<0.001$) and 17% increase in knee flexor muscle strength (0.06±0.2Nm/kg; $p<0.001$) at two years. At the follow up assessment, the time completing the stairs test decreased in the study group ($p=0.039$) and there was a borderline significant decrease in WOMAC-PF score ($p=0.053$). However, there was no statistically significant change in mean time completing the GUG test ($p=0.871$) at two years.

Associations between changes in muscle strength and changes in activity limitations at two years. Tables 3, 4 and 5 show the crude associations between change in knee muscle strength and change in activity limitations at two years. Increases in average knee muscle strength and knee flexor muscle strength were significantly associated with a decrease in WOMAC-PF score, and a decrease in time (seconds) performing the GUG and the stairs test. After the addition of one possible confounder at the time to the crude models, comorbidities change, NSAIDs change and WOMAC pain change were identified as relevant confounders (i.e., more than 10% change in the crude model regression coefficient for the change in muscle strength). In the multivariable model, adjusted for all relevant confounders, increases in average knee muscle strength and knee flexor muscle strength were still strongly associated with a decrease in WOMAC-PF score, and a decrease in time performing the GUG and the stairs test. In the crude models, an increase in knee extensor muscle strength was significantly associated with a decrease in WOMAC-PF score and a decrease in time performing the stairs test. However, in the fully adjusted models, increase in knee extensor muscle strength was only associated with a decrease in time performing the stairs test.

Possible effect of physical therapy. In an additional analysis, we found that the association between increase in muscle strength and decrease in activity limitations occurred among those subjects who had received physical therapy interventions, and not among subjects not receiving physical therapy (Table 6).

Discussion

The present study showed an association between increase in muscle strength and a decrease in activity limitations in patients with established knee OA at two years. This association suggests that muscle strength may partially explain the between-patients variability in the course of activity limitations. To the best of our knowledge and based on a thorough review of the literature, this is the first observational study which described the longitudinal association between knee muscle strength (extensor and flexor muscles separately, and averaged) and activity limitations in patients with established knee OA.

This study represents an extension of evidence from previous cross-sectional, prediction models and intervention studies (4-6;9;10;12), which have previously reported an association between knee muscle strength and activity limitations. The additional value of the current observational study is the longitudinal association between knee extensor and flexor muscles strength separately, as well as average knee muscle strength, with activity limitations in patients with established knee OA. A longitudinal association was found for increases in average knee muscle strength and in knee flexor muscles strength, and a decrease in all the measures of activity limitations assessed. However, increase in knee extensor muscle strength was associated only with a decrease in the stairs tests, a highly demanding performance activity. Moreover, the overall association found in the present study was confirmed in another longitudinal study carried out by our research group in patients with early OA (31).

Eighty percent of the study population reported to have received some type of physical therapy intervention during the two-year follow up. This could explain the overall increase in muscle strength and decrease in activity limitations in the study group at two years. This interpretation is in line with the observation that the association between increase in muscle strength and decrease in activity limitations was limited to those subjects who had received physical therapy interventions. Previous evidence has suggested that muscle weakness may precede activity limitations in patients with knee OA (7; 10); with improvement seen after muscle strengthening interventions (32-36). The linear relationship between increased muscle strength and decreased activity limitations might be explained by the important role of muscle function in the knee joint. The muscles around the knee control the stop/start of the joint motion, add stability and redistribute joint load. Additionally, an appropriate co-contraction of the knee extensor and knee flexor muscles allows to keep the upright position compensating for gravity during standing or while doing activities (37). Besides the direct association between improvement in muscle strength and decrease in activity limitations that can probably be explained by the participation of 80% of the study group in some kind of physical therapy, it is possible that indirect pathways can also have influenced this relationship. For example, it is probable that an improvement in muscle strength might contribute to an increase in the self-confidence which translates into better performance of activities.

The strength of the association between change in muscle strength and the change in activity limitations was moderate (stairs test r=-0.26, p=0.001 and GUG tests r=-0.23, p=0.005). However, given the small changes in strength and activity limitations, the observed association is of considerable interest. There was stronger association between change in average knee muscle strength and change in performance based tests (stairs test r=-0.26, p=0.001 and GUG test r=-0.23, p=0.005) than with changes in self-reported activity limitations (WOMAC-PF r=-0.16, p=0.031). This might be due to the influence of additional psychosocial factors potentially involved in a self-reported measure such as WOMAC-PF. Increase in knee extensor muscle strength was associated with better performance on the stairs test at two years, while increase in knee flexor muscle strength was associated not only with better performance tests but also with a decrease in self-reported activity limitations at two-year follow up. Knee flexor muscles are usually weaker than knee extensor muscles (38). This strength imbalance is partly due to the larger size of the main knee extensor muscles (quadriceps) compared with the main flexors muscles (hamstrings). Although commonly more attention has been given to the assessment of knee extensor muscles due to their leading role within activity limitations (39-41), the findings of the present study suggest a relevant involvement of knee flexor muscles in activity limitations over time in patients with OA highlighting the importance of incorporating training of these muscles in intervention programs.

Some limitations of this study have to be considered. First, 25% of patients dropped out the study at follow up. However, the relevant baseline characteristics were not statistically different between patients who completed and did not complete the follow up assessment (Table 1), which makes us believe that this loss of patients at follow up did not impact the results of our study. It is possible that the patients who did not attend the follow-up assessment might have had a decline in their overall condition, including a decrease in muscle strength and an increase in activity limitations, which might have prevented them from visiting the assessment centre. On the other hand, the opposite may have taken place as well: patients who experienced an improvement in their condition might no longer be interested in taking part in the study. The loss of patients may thus have caused either an under-or overestimation of our results. Second, it was not possible to collect exact information about the quantity or kind of physical therapy treatment received by the patients. This was due to the fact that the physical therapy treatment reported for the patients did not necessary took place at our rehabilitation centre. Therefore, only dichotomous information about receiving therapy or not (yes/no) was available.

A significant positive change in muscle strength was observed in the group of patients who received (n=149) compared with the group who did not receive (n=37) physical therapy during the follow-up period (data not shown). However, as the group who did not receive physical therapy was very small, no separate analyses were presented. Nevertheless, this potential confounder was considered in the study, and the crude coefficient was not affected after adjusting the model for physical therapy treatment. Key strengths of our study are the large number of patients with knee OA (n=186) studied and a longitudinal design.

From a clinical perspective, the results of this study suggest to further encourage muscle strength training interventions in patients with knee OA. Previous intervention studies have found muscle strength training interventions to be effective to decrease activity limitations in patients with knee OA

(32-36). Nevertheless, the optimal type and amount of exercise to be implemented still need to be further defined. Additionally, these results highlight the importance to train both knee extensor and flexor muscles within the intervention programs. Overall, in patients with OA, an optimal delivery of muscle strength training might contribute to a decrease in activity limitations and to a subsequent decrease in participation restrictions. Nevertheless, further longitudinal observational-studies are needed to test these hypotheses in a larger group of patients with established knee OA. We also suggest to incorporate multiple assessment times over a longer follow up period in order to clearly see the progression of the changes and the associations.

Conclusions

Increase in knee muscle strength, mainly in knee flexor muscles, was associated with a decrease in activity limitations in patients with knee OA two years later. These results suggest that muscle strength may partially explain the between-patients variability in activity limitations over time.

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Competing interests

The author(s) declare that they have no competing interests.

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TABLES

Table 1. Patients' baseline characteristics (n=247)

	Follow up assessment completed	
	Yes (n=186)	**No (n=61)**
Age, years	61(7.3)	62(8.6)
Radiographic OA° K/L score ≥2, n (%)	131(71)	44(73)
BMI, kg/m²	29.3(5.6)	28.8(4.6)
CRP, mg/l	3.4(5.4)	2.5(2.2)
Comorbidities count (CIRS ≥2)	0.8(0.9)	0.6(0.9)
NSAIDs (yes), n (%)	33(18)	7(12)
[a] Knee Muscle strength (Nm/kg)	0.91(0.4)	0.96(0.4)
Knee Extensor muscle strength (Nm/kg)	1.08(0.4	1.15(0.5)
Knee Flexor muscle strength (Nm/kg)	0.73(0.3)	0.78(0.3)
WOMAC pain score (0-20)	7.9(3.8)	7.9(3.0)
WOMAC stiffness score (0-8)	3.7(1.7)	4.1(1.5)
WOMAC physical function score (0-68)	28.6(13.4)	29.8(11.4)
GUG, seconds	11.1(3.8)	10.8(2.3)
Stairs test, seconds	9.1(3.5)	9.4(5.9)

Mean ± standard deviation (sd), unless other stated. OA= osteoarthritis; °K/L= Kellgren/Lawrence. [a]average knee extensor and flexor muscle strength. Baseline characteristics were no significantly different between subgroups.

Table 2. Characteristics of the study population (n=186)

	Baseline		Two years follow up		
	N		n		*p*
Age, years	186	61(7.3)	-	-	-
Female, n(%)	186	127(68)	-	-	-
Radiographic OA, K/L score ≥2, n (%)	184	130(70)	186	123(66)	0.13
K/L score 2, n (%)		58(31)		55(29)	
K/L score 3, n (%)		52(28)		31(17)	
K/L score 4, n (%)		20(11)		37(20)	
BMI, kg/m²	185	29.3(5.5)	186	29.3(5.4)	0.26
Comorbidities count (CIRS ≥2)	184	0.8(1.0)	175	1.1(1.0)	0.00
NSAIDs (yes), n (%)	185	30(16)	186	38(20)	0.23
CRP, mg/l	183	3.4(5.4)	184	2.9(3.1)	0.21
[a] Knee Muscle strength (Nm/kg)	177	0.92(0.4)	183	0.98(0.4)	0.00
Knee Extensor muscle strength (Nm/kg)	179	1.1(0.5)	185	1.2(0.5)	0.00
Knee Flexor muscle strength (Nm/kg)	181	0.7(0.3)	184	0.8(0.3)	0.00
WOMAC pain score (0-20)	183	7.9(3.8)	185	7.0(4.3)	0.01
WOMAC stiffness score (0-8)	179	3.7(1.7)	186	3.5(2.0)	0.02
WOMAC physical function score (0-68)	183	28.6(13.4)	186	27.0(15.3)	0.05
GUG, seconds	185	11.0(3.6)	185	10.9(5.0)	0.87
Stairs test, seconds	185	15.1(8.8)	181	13.7(7.3)	0.04
PT treatment during the past 2 years (yes), n (%)	-	No information	186	149(80)	-

Mean ± standard deviation (sd), unless other stated. OA= osteoarthritis; K/L= Kellgren/Lawrence, CRP=C-reactive protein, PT= physiotherapy. [a]average knee extensor and flexor muscle strength.

Table 3. Association between knee muscle strength change and changes in activity limitations over two years

	WOMAC-PF score (0-68)			GUG Test (seconds)			Stairs Test (seconds)		
	b	**95% CI**	**p-value**	**b**	**95% CI**	**p-value**	**b**	**95% CI**	**p-value**
1 **Crude model**									
Knee muscle strength (KMS) change	-9.5	-16.7,-2.3	0.01	-1.8	-3.0,-0.5	0.01	-4.4	-6.5,-2.3	<0.001
2 **Adjusted Models**									
KMS change + gender	-9.4	-16.6,-2.2	0.01	-1.7	-2.9,-0.5	0.01	-4.4	-6.5,-2.3	<0.001
KMS change + age	-9.2	-16.3,-2.2	0.01	-1.8	-3.0,-0.6	0.004	-4.4	-6.5,-2.3	<0.001
KMS change + BMI change	-9.1	-16.3,-1.9	0.01	-1.8	-3.0,-0.5	0.01	-4.4	-6.5,-2.3	<0.001
KMS change + CRP change	-9.3	-16.5,-2.0	0.01	-1.7	-3.0,-0.5	0.01	-4.3	-6.5,-2.2	<0.001
KMS change + comorbidities change	-9.4	-17.0,-1.9	0.01	-1.4*	-2.5,-0.3	0.01	-4.2	-6.5,-2.0	<0.001
KMS change + NSAIDs change	-9.1	-16.3,-1.9	0.01	-1.6*	-2.8,-0.4	0.01	-4.4	-6.5,-2.3	<0.001
KMS change + WOMAC pain change	-5.7*	-10.9,-0.5	0.03	-1.5*	-2.5,-0.4	0.01	-4.2	-6.2,-2.2	<0.001
KMS change + PT treatment	-9.3	-16.7,-2.0	0.01	-1.7	-3.0,-0.5	0.01	-4.3	-6.4,-2.2	<0.001
3 **Fully Adjusted Model**									
KMS change	-5.7 [B1]	-10.9,-0.5	0.03	-1.2 [B2]	-2.3,-0.1	0.03	-4.4 [B3]	-6.5,-2.3	<0.001

Linear regression analysis using change in knee muscle strength (average extensor and flexor) as independent factor. Changes in WOMAC-PF (Webster Ontario and McMaster Osteoarthritis index-Physical Function), Get Up and Go test (GUG), time walking up and down a lap of 12 stairs as dependent variables. b = Regression coefficient; CI = confidence interval. CRP= c-reactive protein; NSAIDs= use of anti-inflammatory drugs; PT= physiotherapy treatment. All the models were adjusted for the baseline activity limitations (analysis of covariance). *Factor affects the coefficient 10% or more. Reduce patients numbers in the multivariate linear regression analyses due to random missing in the outcome measure or selected variables.

1 Crude Model

2 Adjusted Model for relevant confounders.

3 Full Adjusted Model for factors affecting the crude coefficient 10% or more: B1 adjusted for WOMAC pain change and baseline WOMAC-PF; B2 adjusted for comorbidities change, NSAIDS change, WOMAC pain change and baseline GUG test; B3 adjusted for baseline stairs test.

Table 4. Association between knee extensor muscle strength change and changes in activity limitations over two years

	WOMAC-PF score (0-68)			GUG Test (seconds)			Stairs Test (seconds)		
	b	95% CI	p-value	b	95% CI	p-value	b	95% CI	p-value
1 **Crude model**									
Knee extensor muscle strength (EMS) change	-5.9	-11.2,-0.7	0.03	-0.9	-2.0,0.1	0.08	-2.7	-4.2,-1.1	0.001
2 **Adjusted Models**									
EMS change + gender	-6.0	-11.2,-0.7	0.03	-1.0*	-2.0,0.1	0.07	-2.7	-4.2,-1.1	0.001
EMS change + age	-5.9	-11.1,-0.7	0.03	-0.9	-2.0,0.1	0.08	-2.7	-4.2,-1.1	0.001
EMS change + BMI change	-5.7	-11.0,-0.4	0.03	-0.9	-1.9,0.2	0.10	-2.6	-4.2,-1.1	0.001
EMS change + CRP change	-5.1*	-10.5,0.3	0.06	-0.8*	-1.9,0.3	0.15	-2.7	-4.3,-1.1	0.001
EMS change + comorbidities change	-5.6	-11.0,-0.2	0.04	-0.9	-1.9,0.1	0.09	-2.6	-4.2,-1.0	0.002
EMS change + NSAIDs change	-5.7	-11.0,-0.4	0.03	-0.9	-1.9,0.2	0.10	-2.7	-4.2,-1.1	0.001
EMS change + WOMAC pain change	-3.8*	-7.5,0.01	0.05	-0.9	-2.0,0.1	0.07	-2.6	-4.1,-1.1	0.001
EMS change + PT treatment	-5.8	-11.1,-0.4	0.04	-0.9	-2.0,0.1	0.09	-2.6	-4.1,-1.0	0.001
3 **Fully Adjusted Model** EMS change	-2.8 [B1]	-6.6,1.0	0.15	-0.8 [B2]	-1.9,0.2	0.12	-2.7 [B3]	-4.2,-1.1	0.001

Linear regression analysis using change in knee extensor muscle strength as independent factor. Changes in WOMAC-PF (Webster Ontario and McMaster Osteoarthritis index-Physical Function), Get Up and Go test (GUG), time walking up and down a lap of 12 stairs as dependent variables. b = Regression coefficient; CI = confidence interval. CRP= c-reactive protein; NSAIDs= use of anti-inflammatory drugs; PT= physiotherapy treatment. All the models were adjusted for the baseline activity limitations (analysis of covariance). *Factor affects the coefficient 10% or more. Reduce patients numbers in the multivariate linear regression analyses due to random missing in the outcome measure or selected variables.

1 Crude Model

2 Adjusted Model for relevant confounders.

3 Full Adjusted Model for factors affecting the crude coefficient 10% or more: B1 adjusted for CRP change, WOMAC pain change and baseline WOMAC-PF; B2 adjusted for gender, CRP change and baseline GUG test; B3 adjusted for baseline stairs test.

Table 5. Association between knee flexor muscle strength change and changes in activity limitations over two years

		WOMAC-PF score (0-68)			GUG Test (seconds)			Stairs Test (seconds)		
		b	**95% CI**	**p-value**	**b**	**95% CI**	**p-value**	**b**	**95% CI**	**p-value**
1	**Crude model**									
	Knee flexor muscle strength (FMS) change	-13.9	-22.3,-5.5	0.001	-1.9	-3.4,-0.4	0.01	-7.3	-10.3,-4.4	<0.001
2	**Adjusted Models**									
	FMS change + gender	-13.8	-22.3,-5.4	0.001	-1.9	-3.4,-0.4	0.01	-7.4	-10.4,-4.5	<0.001
	FMS change + age	-13.6	-21.9,-5.3	0.001	-1.9	-3.4,-0.4	0.01	-7.3	-10.3,-4.4	<0.001
	FMS change + BMI change	-13.4	-21.9,-5.0	0.002	-1.9	-3.4,-0.4	0.01	-7.3	-10.3,-4.3	<0.001
	FMS change + CRP change	-12.8	-21.2,-4.5	0.003	-1.7*	-3.2,0.2	0.03	-7.1	-10.1,-4.2	<0.001
	FMS change + comorbidities change	-14.7	-23.7,-5.8	0.001	-2.0	-3.4,-0.6	0.01	-7.5	-10.8,-4.3	<0.001
	FMS change + NSAIDs change	-13.1	-21.3,-4.7	0.003	-1.6*	-3.0,-0.1	0.03	-7.3	-10.3,-4.3	<0.001
	FMS change + WOMAC pain change	-6.2*	-12.3,-0.1	0.05	-1.8	-3.1,-0.5	0.01	-6.6*	-9.5,-3.7	<0.001
	FMS change + PT treatment	-14.1	-22.8,-5.3	0.002	-1.9	-3.4,-0.3	0.02	-7.2	-10.3,-4.2	<0.001
3	**Fully Adjusted Model**									
	FMS change	-6.2 [B1]	-12.3,-0.1	0.05	-1.4 [B2]	-2.9,0.01	0.05	-6.6 [B3]	-9.5,-3.7	<0.001

Linear regression analysis using change in knee flexor muscle strength as independent factor. Changes in WOMAC-PF (Webster Ontario and McMaster Osteoarthritis index-Physical Function), Get Up and Go test (GUG), time walking up and down a lap of 12 stairs as dependent variables. b = Regression coefficient; CI = confidence interval. CRP= c-reactive protein; NSAIDs= use of anti-inflammatory drugs; PT= physiotherapy treatment. All the models were adjusted for the baseline activity limitations (analysis of covariance). *Factor affects the coefficient 10% or more. Reduce patients numbers in the multivariate linear regression analyses due to random missing in the outcome measure or selected variables.

1 Crude Model

2 Adjusted Model for relevant confounders.

3 Full Adjusted Model for factors affecting the crude coefficient 10% or more: B1 adjusted for WOMAC pain change and baseline WOMAC-PF; B2 adjusted for CRP change, NSAIDS change and baseline GUG test; B3 adjusted for WOMAC pain change and baseline stairs test.

Table 6. Association between knee muscle strength change and changes in activity limitations over two years n=186

	WOMAC-PF score (0-68)			**GUG Test (seconds)**			**Stairs Test (seconds)**		
	b	**95% CI**	**p-value**	**b**	**95% CI**	**p-value**	**b**	**95% CI**	**p-value**
Subjects reporting PT treatment (n=149)									
Knee muscle strength (FMS) change	-10.3	-18.1,-2.4	0.011	-1.7	-3.2,-0.4	0.010	-4.4	-6.8,-2.1	<0.001
Knee extensor muscle strength (FMS) change	-6.9	-12.8,-1.1	0.020	-1.0	-2.2,0.2	0.095	-2.9	-4.6,-1.2	0.001
Knee flexor muscle strength (FMS) change	-14.5	-23.8,-5.1	0.003	-2.0	-3.7,-0.3	0.021	-7.1	-10.5,-3.8	<0.001
Subjects not reporting PT treatment (n=37)									
Knee muscle strength (FMS) change	-3.9	-25.7,17.7	0.714	-1.7	-4.7,1.2	0.239	-2.9	-8.5,2.8	0.308
Knee extensor muscle strength (FMS) change	-0.9	-14.7,12.9	0.901	-0.8	-2.7,1.0	0.396	-1.0	-4.5,2.6	0.576
Knee flexor muscle strength (FMS) change	-10.7	-37.3,15.8	0.417	-1.2	-5.1,2.6	0.507	-3.8	-10.9,3.2	0.278

Linear regression analysis using change in knee muscle strength as independent factor. Changes in WOMAC-PF (Webster Ontario and McMaster Osteoarthritis index-Physical Function), Get Up and Go test (GUG), time walking up and down a lap of 12 stairs as dependent variables. b = Regression coefficient; CI = confidence interval. CRP= c-reactive protein; NSAIDs= use of anti-inflammatory drugs; PT= physiotherapy treatment. All the models were adjusted for the baseline activity limitations (analysis of covariance).

FIGURES

Figure 1. Patients course during the study.